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Glasgow Coma Scores, Early Opioids, and Posttraumatic Stress Disorder Among Combat Amputees

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A recent study found that combat amputees had a reduced prevalence of posttraumatic stress disorder (PTSD) compared with nonamputees with serious extremity injuries. We hypothesized that an extended period of impaired consciousness or early treatment with morphine could prevent consolidation of traumatic memory and the development of PTSD. To examine this hypothesis, we retrospectively reviewed 258 combat casualty records from the Iraq or Afghanistan conflicts from 2001–2008 in the Expeditionary Medical Encounter Database, including medications and Glasgow Coma Scale (GCS) scores recorded at in-theater facilities within hours of the index injury. All patients sustained amputations from injuries. Psychological diagnoses were extracted from medical records for 24 months postinjury. None of 20 patients (0%) with GCS scores of 12 or lower had PTSD compared to 20% of patients with GCS scores of 12 or greater who did have PTSD. For patients with traumatic brain injury, those treated with intravenous morphine within hours of injury had a significantly lower prevalence of PTSD (6.3%) and mood disorders (15.6%) compared to patients treated with fentanyl only (prevalence of PTSD = 41.2%, prevalence of mood disorder = 47.1%). GCS scores and morphine and fentanyl treatments were not significantly associated with adjustment, anxiety, or substance abuse disorders.

Among military service members, combat injury is significantly associated with increased likelihood of psychological disorders, including posttraumatic stress disorder (PTSD) (Hoge, Terhakopian, Castro, Messer, & Engel, 2007; MacGregor et al., 2009; Pittman, Goldsmith, Lemmer, Kilmer, & Baker, 2011). Postinjury care can be greatly complicated by PTSD; therefore, its prevention remains a priority for military providers (Hoge et al., 2007; Pittman et al., 2011). Although amputations are among the most serious battle injuries, a recent study found a reduced prevalence of PTSD among combat amputees relative to nonamputees with serious extremity injuries (Melcer et al., 2013). This novel finding suggests that certain injury characteristics and/or postinjury care factors for combat amputees may be protective against PTSD.

Amnesic events, including an extended period of impaired or loss of consciousness, may reduce the likelihood of PTSD. The relationship between traumatic brain injury (TBI) and PTSD outcomes, however, has been inconsistent (Hoge et al., 2008; MacGregor et al., 2010; Schneiderman, Braver, & Kang, 2008). The Glasgow Coma Scale (GCS) is an established measure used to assess the patient's brain injury following trauma (Teasdale & Jennett, 1974). The GCS provides scores ranging from 3 to 15, with scores of 3 to 12 indicating moderate or severe TBI. Little research has investigated postinjury GCS scores and psychological outcomes, particularly in recent combat populations (Chiu, deRoon-Cassini, & Brasel, 2011; Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010).

Medications such as opioids administered shortly after trauma may also prevent PTSD by decreasing pain and/or interfering with memory consolidation for the traumatic event (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009; McGhee et al., 2011; Steckler & Risbrough, 2012; Stoddard et al., 2009). Among combat casualties, morphine administered

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Table 1
Comparison of Demographic/Injury Characteristics for Study Samples by Levels of Care Versus All Amputees Injured 2001–2008

	Levels 1–4 medication $n = 258$		Level 2 medication $n = 148$		All amputees $N = 857$	
Variable	*n*	%	*n*	%	*n*	%
Age < 25 years	165	64.0	103	69.6	483	56.4
Preinjury psychological diagnosis	26	10.1	8	5.4	91	10.6
Blast injury	249	96.5	141	95.3	797	93.0
TBI	115	44.6	63	42.6	324	37.8
Unilateral amputation	188	72.9	109	73.6	660	77.0
Lower limb amputation	217	84.1	119	80.4	702	81.9
Injury year 2001–2006	170	65.9	120	81.1	552	64.4
PTSD	59	22.9	25	16.9	178	20.8

Note. Tables exclude cases with missing data (under 5.0% for all variables). PTSD = posttraumatic stress disorder; TBI = traumatic brain injury.

soon after injury was significantly associated with decreased likelihood of PTSD by approximately 50% (Holbrook et al., 2010). Morphine and fentanyl are used routinely for early pain management following combat injuries, but there has been substantial debate concerning which of these medications might be the most appropriate (Black & McManus, 2009; Kacprowicz, Johnson, & Mosely, 2008). Little research has compared how morphine and fentanyl might impact later psychological outcomes such as PTSD.

In the present study, we investigated the relationship in combat amputees between early postinjury sequelae such as impaired consciousness, pain medications, and later psychological outcomes, particularly PTSD. Based on previous studies (Bryant et al., 2009; Holbrook et al., 2010; Stoddard et al., 2009), we hypothesized that management of pain and anxiety with intravenous morphine within hours of injury would protect against the development of PTSD. We also hypothesized that early posttrauma GCS scores of 12 or less or medically induced loss of consciousness (via sedatives, paralytics, and/or sedatives) would interfere with the formation of traumatic memory and reduce the prevalence of PTSD.

Method

Participants

We searched the military health databases below to identify 857 U.S. military personnel with major limb amputations (excluding fingers, toes) following combat injuries in the Afghanistan or Iraq conflicts from 2001–2008. This total is over 95% of all U.S. combat amputees during this period (Armed Forces Health Surveillance Center, 2011). Patients with severe brain or spinal injury leading to paralysis were excluded. Of the 857 combat amputees injured through 2008, we identified 258 patients with Level 1, 2, 3, or 4 medication records. Combat care begins near the point of injury with Level 1 (first aid). Subsequently, seriously injured patients are evacuated as soon as possible or within hour(s) of injury to Level 2 facilities for life-saving resuscitation and hemorrhage control. Within 72 hours, patients transfer to Level 3 facilities (e.g., field hospitals) within the combat zone for specialized surgical services. Level 4 facilities provide definitive care outside the combat zone, but within the overall theater of operations (e.g., Landstuhl Regional Medical Center, Germany). Level 5 facilities provide medical care within the United States.

The study sample ($n = 258$) was a subset of amputees injured in 2001–2008 ($N = 857$). Of the 258 patients, there were the only 148 amputees who had Level 1 or 2 medication records. Another 100 amputees were included to increase power for analyses of Level 3 or 4 medication records. The study sample generally consisted of relatively young individuals who sustained unilateral, lower limb amputations following blast injuries, similar to the overall population of amputees (Table 1). Injury Severity Scores (median ISS: Level 2 = 17.00, Levels 1–4 = 16.00, all 857 amputees = 14.00) and TBI prevalence for the overall population and the present study samples also were similar. The subsample of patients with Level 1 or 2 medication data were more likely to have been injured before 2007 and had numerically lower prevalence of a preinjury psychological diagnosis and postinjury PTSD than the overall identified population of 857 amputees.

Procedure

The Expeditionary Medical Encounter Database (Galarneau et al., 2006), formerly known as the Navy–Marine Corps Combat Trauma Registry, gathers data from Navy–Marine Corps Level 1, 2, and 3 medical facilities, supplemented by Level 3 data from the Theater Medical Data Store and Level 4 and 5 facilities treating all military services. The Expeditionary Medical Encounter Database uses clinical encounter forms to capture patients' time of arrival at treatment facilities, mechanism of

injury, injury descriptions, GCS scores, and medications with associated dosages, and routes of administration. Given the limited time available for Level 2 providers to record information, providers noted pain intensity ratings (i.e., 0–10, 10 = most severe pain) for only three patients in this study (one score of 9, two scores of 10). The encounter forms are completed by providers in theater either on paper or electronically and are forwarded to the Expeditionary Medical Encounter Database at the Naval Health Research Center. Our clinicians use the encounter forms to calculate ISSs (Copes et al., 1998). The study was approved by the Institutional Review Board at the Naval Health Research Center (NHRC.2007.0016).

Combat amputees and their associated anatomical levels of amputations (e.g., upper or lower limb) and subsequent psychological outcomes were identified by searching military health databases, including Standard Inpatient Data Records, Standard Ambulatory Data Records, and Health Care Service Record files for the ninth revision of the *International Classification of Diseases* (ICD-9) diagnostic codes via TRICARE Management Activity at Level 4 and 5 medical facilities (Hart, Stegman & Ford, 2008).

This was a retrospective review of existing medical records of combat amputees injured in 2001–2008 in Iraq or Afghanistan. Patient injuries and psychological outcomes were tracked for 24 months postinjury or until medical records were no longer available in databases (due to military service discharge). Mechanisms of injury were categorized as blast (e.g., improvised explosive device), gunshot wound, and other (e.g., crush injury). ISSs (Copes et al., 1998) were coded directly by Expeditionary Medical Encounter Database clinicians based on data recorded by forward-deployed health care providers. TBI was indicated by the following ICD-9 codes within 30 days of injury: 800.00–801.99 (fractures of the vault or base of the skull), 803.00–804.99 (other unqualified and multiple fractures of the skull), 850.00–854.10 (intracranial injury, including concussion, contusion, laceration, and hemorrhage; Centers for Disease Control and Prevention, 2012a). These TBI codes did not distinguish between mild, moderate, or severe cases.

GCS scores, medication type, dosage, and route of administration and associated level of care were extracted from in-theater patient encounter forms by Expeditionary Medical Encounter Database trauma nurses. GCS scores of 3 to 12 indicate moderate to severe TBI (Centers for Disease Control and Prevention, 2012b). The medications evaluated are listed in Table 2. We found dosages for at least some medications for 91.0% of patients. The U.S. military has established policies for recording of controlled medications (e.g., morphine, fentanyl), which are carefully logged by physicians (Benedek, Schnieder, & Bradley, 2007).

Preinjury psychological diagnoses were recorded in military databases based on routine provider interviews with patients during inpatient and outpatient encounters at military treatment facilities and government-reimbursed private clinics. Postinjury psychological diagnoses were identified in military databases by ICD-9 codes between 290–319. The primary outcome was at least two separate PTSD diagnoses (ICD-9 code 309.81) or not, based on separate clinical encounters within 24 months postinjury. Records were merged from the Armed Forces Health Longitudinal Technology Application. Patients with at least two PTSD diagnoses (vs. one) recorded in health databases are more likely to have a criterion score of ≥ 50 for PTSD on the PTSD Checklist-Military Version (Gravely et al., 2011). We note that patient surveys that screen for PTSD (e.g., PTSD Checklist-Military Version) help validate clinician diagnoses of PTSD. One limitation of such surveys, however, is that they sometimes produce false-positives for PTSD, particularly among patients with severe TBI (Sumpter & McMillan, 2006). The remaining psychological diagnoses were grouped as adjustment, anxiety, mood, substance abuse disorders, and other psychological diagnoses. Other psychological diagnoses included postconcussion syndrome, pain, and sleep disorders.

Data Analysis

Sample sizes for analyses of data varied by the level of care at which medications were administered. Patients were excluded from analyses of specific levels of care for which they had no

Table 2
Number of Patients Receiving Medications and Associated Dosages Across Levels of Care

			Most frequent within class			Dosage recorded		Dosage range (percentile)		
Medication class	*n*	%		*n*	%	*n*	%	15%	50%	85%
Antibiotics	241	93.4	Cefazolin	214	82.9	185 of 214	86.4	1.00 g	1.00 g	2.00 g
Paralytics	85	32.9	Succinylcholine	84	32.6	61 of 84	72.6	100.00 mg	100.00 mg	150.00 mg
Muscle relaxants	97	37.6	Vecuronium bromide	95	36.8	71 of 95	74.7	3.00 mg	10.00 mg	10.00 mg
Analgesics	249	96.5	Morphine	200	77.5	122 of 200	61.0	2.00 mg	5.00 mg	10.00 mg
			Fentanyl	193	74.8	133 of 193	68.9	50.00 mcg	50.00 mcg	100.00 mcg
Sedatives/amnesic	137	53.1	Midazolam	122	47.3	77 of 122	63.1	2.00 mg	3.00 mg	5.00 mg
General anesthetics	138	53.5	Etomidate	71	27.5	53 of 71	74.6	13.00 mg	20.00 mg	20.00 mg

Note. $N = 258$. Intravenous was the most frequent route of administration. Route of administration and dosage data were not recorded for 22.6% of administered medications.

Table 3
Postinjury PTSD Outcomes by Selected Level 2 Opioid Treatment

Level 2 medication	Total cases	PTSD cases	PTSD %	ISS median	GCS < 12 %
Neither morphine nor fentanyl	30	2	6.7	24.00	20.0
Fentanyl only	32	10	31.3	14.00	12.5
Any morphine	83	12	14.5	14.00	12.0
Morphine only	57	10	17.5	14.00	8.8
Morphine and fentanyl	26	2	7.7	17.00	19.2
Total	145	24	16.6	17.00	13.8

Note. PTSD cases included only patients with at least two separate PTSD diagnoses.
GCS = Glasgow Coma Score; ISS = Injury Severity Score; PTSD = posttraumatic stress disorder. Patients with Level 2 medication records, $n = 142$; patients with Level 1 medication records, $n = 3$.

records (e.g., Level 2). Patients with Level 1 or 2 medication data were analyzed separately from subsequent levels of care ($n = 148$). Chi-square tests were used ($p < .05$ or $p < .01$) to test associations between variables except where Fisher's exact test were indicated as appropriate for cell sizes less than five. Level 2 GCS scores indicated either mild (GCS scores of 13–15), moderate (GCS scores of 9–12) or severe TBI (GCS score of 3–8). GCS scores of 3–12 indicating both moderate and severe TBI were combined due to the small number of patients with GCS scores of < 12. Logistic regressions were conducted to determine whether medications (e.g., morphine vs. fentanyl) were significantly associated with patients' PTSD status, adjusting for covariates, including ISS and year of injury.

Results

A low GCS score of 12 or less (vs. GCS score of 13–15) was significantly associated with reduced prevalence of PTSD (Fisher's exact test, $p = .019$) but increased prevalence of other psychological diagnoses (e.g., pain, postconcussion syndrome; $p = .016$). GCS scores of 12 or less, however, were not significantly associated with prevalence of adjustment, anxiety, mood, or substance abuse disorders.

Approximately half of patients (57.4 %, $n = 148$) had Level 1 or 2 medication records (including only three patients with Level1 medication records). The earliest medication records available for another one third of patients were at Level 3 (35.6%, $n = 92$), and the remaining patients had only Level 4 medication records (6.9%, $n = 18$). Across levels of care, the most frequently administered medications were intravenous antibiotics and opioid analgesics. Morphine and fentanyl were the most frequently administered intravenous analgesics (Table 2). Subsequentanalyses used a Level 2 medication group of 145 patients (excluding 3 of the 148 patients in the Level 2 medication group because they had no PTSD outcomes). Of the 145 patients in this Level 2 medication group, 115 received morphine and/or fentanyl and 77.4% (89 of 115) of these patients had dosage data.

For the Level 2 medication group, the median value for the highest dose administered by patient was 10.00 mg for morphine and 100.00 mcg for fentanyl. Our clinicians and previous literature verified that these dosages are effective to reduce severe pain (Fox, Saunders, Menk, & Middaugh, 1995). Because the analgesic effect of fentanyl is approximately 100 times more than morphine, the median Level 2 dosages administered to patients for these opioids appeared equivalent for analgesic effectiveness (Fox et al., 1995). Of the morphine-treated patients with dosage information, only 3 of 62 patients received no more than a 2.00-mg dose of morphine at Level 2. Of the fentanyl-treated patients with dosages recorded, only 1 of 43

Table 4
ISS and Prevalence of TBI and Psychological Disorders by Level 2 Opioid Treatment

	TBI		PTSD		Adjustment		Anxiety		Mood		Substance abuse		Other MH		ISS
Level 2 medication	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	(median)
Fentanyl only	17	53.1	10	31.3*	12	37.5	10	31.3	11	34.4**	5	15.6	13	40.6	14.00
Any morphine	32	38.6	12	14.5*	29	34.9	25	30.1	14	16.9**	10	12.0	39	47.0	14.00

Note. Fentanyl only, $N = 32$; any morphine. $N = 83$. PTSD cases included only patients with at least two separate PTSD diagnoses. ISS = Injury Severity Score; MH = mental health; PTSD = posttraumatic stress disorder; TBI = traumatic brain injury.
*Level 2 medication by PTSD association statistically significant (chi-square tests, $p < .05$). **Level 2 medication by mood association statistically significant (chi-square tests, $p < .05$).

Table 5
TBI Diagnosis, Level 2 Opioid Treatment, and PTSD and Mood Disorders

	TBI				No TBI			
	Any morphine ($n = 32$)		Fentanyl ($n = 17$)		Any morphine ($n = 51$)		Fentanyl ($n = 15$)	
Variable	*n*	%	*n*	%	*n*	%	*n*	%
PTSD	2	6.3	7	41.2**	10	19.6	3	20.0
Mood	5	15.6	8	47.1*	9	17.6	3	20.0

Note. Significant association between morphine/fentanyl and PTSD (Fisher's exact test, $p < .01$) and mood diagnoses (chi-square test, $p < .05$), among TBI groups. PTSD cases included only patients with at least two separate PTSD diagnoses. PTSD = posttraumatic stress disorder; TBI = traumatic brain injury.
*$p < .05$. **$p < .01$.

received no more than 25.00 mcg dose of fentanyl. (Of the 89 patients with Level 2 opioid-dosage data, 16 patients had both morphine and fentanyl dosages available).

Morphine, Fentanyl, and Psychological Diagnoses

Table 3 shows patients treated with morphine and/or fentanyl at Level 2 and their associated PTSD, ISS, and GCS outcomes. Patients who received morphine alone or morphine combined with fentanyl had lower prevalence of PTSD compared with patients who received fentanyl only (without morphine). Notably, these groups also had similar ISSs and GCS scores. Patients who received neither morphine nor fentanyl (no opioids) had the highest ISSs and the lowest GCS scores and prevalence of PTSD of all four groups. Our Expeditionary Medical Encounter Database clinicians conducted further review of Level 2 charts including provider notes of medically (e.g., intubation procedures) or injury-related loss of consciousness. Patients who received no opioids had significantly higher prevalence of provider-documented loss of consciousness (50.0%; 15 of 30) than patients who did receive opioids (11.3%; 13 of 115, $p < .001$). There was only a trend, however, for lower prevalence of PTSD among patients with provider-documented loss of consciousness (prevalence of PTSD = 7.1%; 2 of 28) compared with patients without loss of consciousness (PTSD = 18.8%; 22 of 117; $p = .081$).

The overall association between the four medication groups (morphine only, fentanyl only, morphine and fentanyl, neither morphine nor fentanyl) and PTSD status as shown in Table 3 was statistically significant (Fisher's exact test, $p = .045$). Preinjury psychological diagnoses and prevalence of TBI diagnoses did not differ significantly among the four groups. The above analyses were repeated for patients who had Level 3 medication data available ($n = 116$), and there was no significant association between medication group and PTSD outcomes.

The results provided in Table 3 show that Level 2 morphine alone, or combined with fentanyl, was associated with reduced prevalence of PTSD. Subsequently, we combined morphine-treated groups (morphine alone or morphine and fentanyl) to increase sample sizes for analysis. The results given in Tables 4 and 5 were similar whether the morphine groups were combined or not. In Table 4, we compare the prevalence of PTSD and other psychological diagnoses for patients who received any morphine (alone or combined with fentanyl) versus individuals who received fentanyl only. These two groups had no significant differences in age or prevalence of preinjury psychological diagnoses. Morphine-treated patients had a significantly lower prevalence of PTSD than patients treated with fentanyl only ($p = .040$). After adjusting for ISS and injury year, morphine alone or combined morphine/fentanyl had significantly reduced odds of PTSD ($OR = 0.37$, CI = [0.14–0.98]) compared to fentanyl only ($p = .045$). The any morphine group (vs. fentanyl only) also had a significantly reduced prevalence of mood disorders ($p = .041$), but these two groups had similar prevalence of adjustment, anxiety, and substance abuse disorders.

Table 5 shows patients treated with any morphine or fentanyl at Level 2 by their TBI status. There was no significant difference between the ISS of the morphine and fentanyl groups for TBI patients (median ISS: morphine = 17.00, fentanyl = 17.00) or no TBI patients (median ISS: morphine = 14.00, fentanyl = 10.00). For patients with a TBI diagnosis, any morphine (vs. fentanyl only) was associated with significantly reduced prevalence of PTSD. For patients without TBI, however, there was no significant association between morphine (vs. fentanyl only) and PTSD. There was no significant difference between median ISS.

We conducted similar analyses as described above to explore relationships between Level 2 antibiotics, paralytics, sedatives and anesthetics, and psychological outcomes. We found no significant associations between these medications and PTSD outcomes. Sample sizes were small, therefore, these negative results should be interpreted with caution.

Discussion

The present study is one of the first to investigate early postinjury sequelae and care factors for combat amputees as they relate to later psychological outcomes, especially PTSD. The major findings were that reduced prevalence of

PTSD was significantly associated with both low GCS scores indicating moderate to severe TBI, and early intravenous morphine or intravenous morphine combined with fentanyl (vs. fentanyl treatment alone). Importantly, this second finding was specific to TBI patients who received opioids (morphine and/or fentanyl) at Level 2 combat care within hours of injury. Interestingly, patients who received no opioids at Level 2 had the lowest prevalence of PTSD and the highest ISS. By contrast, low GCS scores and early intravenous opioid medications were not significantly associated with anxiety, adjustment, or substance abuse disorders. Finally, we found no significant associations between other medications used for care of combat casualties, including paralytics, muscle relaxants, and sedatives and psychological disorders.

The present finding that GCS scores (indicating moderate or severe TBI) were associated with reduced prevalence of PTSD was consistent with some previous studies (Hoge et al., 2008; MacGregor et al., 2010; Schneiderman et al., 2008). Most important, the present findings extended a previous report (Holbrook et al., 2010) in several important ways. First, morphine (alone or combined with fentanyl) was associated with reduced the prevalence of PTSD specifically by comparison to fentanyl alone. Second, we found that morphine reduced the prevalence of PTSD specifically among patients with a TBI diagnosis. The relationship between TBI and PTSD is not completely understood, and given the small sample sizes, the present findings on TBI, intravenous morphine, fentanyl, and PTSD (Table 5) should be interpreted with caution. Third, the relationship between intravenous morphine and PTSD was significant when this medication was administered at combat care Level 2, but not at subsequent levels of care typically more than 24 hours postinjury. Finally, we found that early postinjury intravenous morphine was significantly associated with reduced prevalence of mood disorder as well as PTSD (Tables 4 and 5). Patients with PTSD also have an increased likelihood of mood disorders (Brown, Campbell, Lehman, Grisham, & Mancill, 2001). We hypothesize that fewer morphine-treated patients developed PTSD and therefore they were less likely to develop mood disorders.

The primary clinical implication of the present results is that combat care physicians may consider PTSD prevention as a potential benefit of choosing early intravenous morphine (alone or combined with intravenous fentanyl) versus intravenous fentanyl alone (Black & McManus, 2009; Kacprowicz et al., 2008). Our data support the hypothesis that intravenous opioids (morphine or morphine combined with fentanyl) interfere with the early postinjury neurological processes required for long-term memory of combat trauma and thereby protect against later PTSD (Steckler & Risbrough, 2012). Further research, however, should investigate why early morphine (alone or combined with fentanyl) may have reduced prevalence of PTSD specifically by comparison to fentanyl alone. Morphine and fentanyl have at least some differences in the specific types of opioid receptors in the brain (Pasternak, 2012). Recent animal models of PTSD identified specific morphine-related receptors in the amygdala, which appear to block memory for learned responses to aversive stimuli (e.g., foot shock, immobilization; Andero et al., 2013). Therefore, one hypothesis is that morphine receptors may be more directly involved in memory storage/consolidation than fentanyl receptors. Alternatively, morphine may be more effective in PTSD prevention than fentanyl because morphine has sustained and longer-lasting effects on opioid receptors.

A related explanation is based on the well-established observation that fentanyl produces more rapid onset and offset for pain relief compared to morphine. By contrast, morphine produces longer-lasting pain relief (Fox et al., 1995). Therefore, fentanyl-treated patients may have experienced more intermittent pain between doses, whereas morphine-treated patients had more continuous and longer-lasting pain relief. Consequently, PTSD was more likely among fentanyl-treated patients because they experienced more pain. The pain aspect of this hypothesis is supported by a randomized trial using intravenous morphine or fentanyl doses. Pain relief was similar between morphine and fentanyl treated patients until 40–60 minutes after surgery. Thereafter, morphine-treated patients reported less pain than fentanyl treated patients but PTSD was not assessed (Claxton, McGuire, Chung, & Cruise, 1997).

The results for the two small samples have intriguing clinical implications. First, combined treatment with morphine and fentanyl was significantly associated with lower prevalence of PTSD than fentanyl alone. Some authors hypothesize that combined treatment with multiple opioids (e.g., morphine and fentanyl) may produce more effective pain relief at lower overall dosage (with fewer side effects such as reduced blood pressure) compared to treatment with a single opioid (e.g., morphine only; Pasternak, 2012). Second, patients who received neither morphine nor fentanyl (i.e., no opioids) also had significantly lower prevalence of PTSD than patients treated with fentanyl only. This no-opioids group had the highest injury severity and was significantly more likely to have provider-documented factors typically inducing unconsciousness (e.g., shock, intubation). There was only a trend, however, for lower prevalence of PTSD among any patients with loss of consciousness compared to patients without provider-documented loss of consciousness. Further study should investigate why patients who received no opioids had the lowest prevalence of PTSD in this study.

As mentioned, both intravenous morphine and intravenous fentanyl have the potential for side effects that may negatively impact hemodynamics (Fox et al., 1995). Combat-trauma anesthesiologists are advised to minimize these side effects when managing the most seriously injured and/or hemodynamically unstable patients. The present findings are consistent with this principle of combat casualty care by showing that a subset of combat amputees received neither morphine nor fentanyl, and that these patients had substantially higher ISSs than the morphine and fentanyl comparison groups.

In the present study, we investigated medications administered near the point of combat injury, one of the earliest opportunities for PTSD prevention. Importantly, patients with serious

extremity injuries routinely receive early, aggressive medical, surgical, and/or rehabilitative care for many months postinjury, which may affect PTSD (Wain, Bouterie, & Oleshansky, 2009). Military amputee care programs may provide psychological benefits from multispecialty therapies including psychiatry and access to advanced prosthetics (Melcer et al., 2013). By contrast, patients who sustain limb-threatening injuries without amputation typically require relatively prolonged rehabilitation specifically including multiple reconstructive surgeries (Wain et al., 2011). Surgeries represent additional trauma and may influence development of PTSD (McGhee et al., 2011).

The primary strength of the present study was the casualty records in the Expeditionary Medical Encounter Database detailing specific patient injuries and early medications. Approximately 90% of all combat amputees received psychiatric care by military physicians, particularly during the first year postinjury (Melcer et al., 2013). Therefore, we expected that patients in the present study were carefully assessed by clinicians for psychological disorders.

The primary study limitation was the small sample sizes. The present study samples, however, appeared to be representative of the overall population of amputees injured in the Iraq and Afghanistan conflicts (2001–2008). Importantly, pain scores were not available before and/or after administration of pain medications. Our clinicians noted that amputees typically experienced serious or severe pain upon arrival to Level 2 care, consistent with the moderate to serious ISSs in this study (median range = 10–24). Blast weapons accounted for over 90% of the injuries; therefore, the present results may not generalize to other traumatic injuries. Because the diagnostic criteria for PTSD overlap with TBI, mood, and postconcussion syndrome, cases of PTSD might have been misdiagnosed (Lew et al., 2008). We included patients with at least two separate PTSD diagnoses at separate health care encounters to avoid false-positives.

Finally, VA health data were not available for the present study. Preliminary analysis of combined VA and military health records for the present study sample yielded similar conclusions. The association between GCS scores and decreased prevalence of PTSD was limited to a nonsignificant trend during the first year postinjury, when military and VA health diagnoses are considered. We are following military and VA health diagnoses for the present study sample for the first 4 years postinjury.

In summary, the present study showed that for patients with serious combat extremity injuries resulting in amputation, GCS scores of 3–12 and early treatment with intravenous morphine alone or combined with fentanyl were associated with reduced prevalence of PTSD. GCS scores and treatment with intravenous morphine were not associated with other psychological outcomes (e.g., adjustment, substance abuse disorders). Other medications routinely used during early care of combat casualties (e.g., paralytics) were not associated with PTSD or other psychological outcomes. Further research should determine the applicability of the present findings to nonamputees with serious extremity injuries.

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14. ABSTRACT (maximum 200 words)
A recent study found that combat amputees had a reduced prevalence of posttraumatic stress disorder (PTSD) compared with nonamputees with serious extremity injuries. We hypothesized that an extended period of impaired consciousness or early treatment with morphine could prevent consolidation of traumatic memory and the development of PTSD. To examine this hypothesis, we retrospectively reviewed 258 combat casualty records from the Iraq or Afghanistan conflicts from 2001–2008 in the Expeditionary Medical Encounter Database, including medications and Glasgow Coma Scale (GCS) scores recorded at in-theater facilities within hours of the index injury. All patients sustained amputations from injuries. Psychological diagnoses were extracted from medical records for 24 months postinjury. None of 20 patients (0%) with GCS scores of 12 or lower had PTSD compared to 20% of patients with GCS scores of 12 or greater who did have PTSD. For patients with traumatic brain injury, those treated with intravenous morphine within hours of injury had a significantly lower prevalence of PTSD (6.3%) and mood disorders (15.6%) compared to patients treated with fentanyl only (prevalence of PTSD = 41.2%, prevalence of mood disorder = 47.1%). GCS scores and morphine and fentanyl treatments were not significantly associated with adjustment, anxiety, or substance abuse disorders.

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